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Interaction of different statins with model membranes by NMR data

L.F. Galiullina *, O.V. Aganova, I.A. Latfullin, G.S. Musabirova, A.V. Aganov, V.V. Klochkov

Kazan (Volga Region) Federal University, 18 Kremlevskaya St., 420008 Kazan, Russian Federation

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ABSTRACT

Hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins reduce the amount of low-density lipoprotein (LDL) cholesterol, which is known as a well-established risk factor for atherosclerosis. Despite the fact that statins have a common pharmacologic target essential to sterol biosynthesis, their efficacy, safety, and potential non-LDL actions vary significantly for different statins. There is a hypothesis that pharmacological features of statins depend on their location in cell membrane, but to the present day there is a lack of information in literature on interactions of statins with the surface of the cell membrane in liquid media. The results of NMR experiments showed that all studied statins form intermolecular complexes with models of cell membranes (dodecylphosphocholine micelles) in water solution. Locations of pravastatin, simvastatin, fluvastatin and cerivastatin on model membranes were established by NOESY NMR data. Distinctions in their positions can explain differences in pharmacological properties of studied compounds.

1. Introduction

Hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins reduce the amount of low-density lipoprotein (LDL) cholesterol, which is known as a well-established risk factor for atherosclerosis. Despite the fact that statins have a common pharmacologic target, which is essential to sterol biosynthesis, their efficiency, safety, and potential non-LDL actions differ considerably depending on their chemical structure. These drugs vary significantly in their rate of absorption, amount of protein binding, degree of renal excretion, metabolism, hydrophilicity, interaction with other drugs, and potency on a per-weight basis [1–5]. Origins of these differences are not well investigated. There is a hypothesis that metabolism and safety of statins depend on their location in the cell membrane [6–8], but to the present day there is a lack of information in literature on interactions of statins with the surface of the cell membrane in liquid media. Therefore, investigation of interaction of statins with cell membrane in solution can shed light on the reasons of their pharmacologic differences.

Nuclear Overhauser Effect NMR spectroscopy (NOESY) is an effective method for studying intermolecular interactions, particularly including different medicines [9–13]. It can provide information on the structure of molecular complex and on certain fragments of the molecule which are responsible for the binding. However, the capabilities of modern NOESY NMR spectroscopy in the field of cell study are still very limited. There is a problem in using this technique for investigation of molecular interactions in phospholipid membranes because T_2 proton relaxation times of phospholipid aggregates are too short relative to the NMR chemical-shift timescale [14–15]. Nevertheless, interactions of different drugs with cell surface can be effectively studied by NMR using model membranes such as dodecylphosphocholine micelles. Zwitterionic dodecylphosphocholine (DPC) are one of the most widely used surfactants for cell membrane modeling in the field of NMR structural biology [16–20]. DPC micelles effectively mimic eukaryotic membranes, because DPC has exactly the same head group as phosphatidylcholines that are predominant class in eukaryotes.

The aim of this work is to study the interaction of statins (pravastatin, simvastatin, fluvastatin, and cerivastatin) having different pharmacological properties [1–5] with models of cell membranes (DPC micelles) by NMR spectroscopy. This paper is an attempt to explain the pharmacological differences of statins in terms of distinctions in their location on the cell membrane.

2. Material and methods

2.1. Samples preparation

All statins and dodecylphosphocholine were purchased from Sigma-Aldrich Rus (Moscow, Russia) and used without further purification. Pravastatin, fluvastatin, and cerivastatin were dissolved in D_2O and D_2O + DPC with concentration of 7.1, 7.3 and 6.5 mM respectively. Simvastatin was dissolved in D_2O + DPC with concentration of 3.1 mM. Solutions containing micelles were prepared using combination of deuterated (>98%) and undeuterated DPC. The concentration of DPC in D_2O solution was greater than the critical micelle concentration and was equal to 7.7 mM for non-deuterated DPC and 17.5 mM for deuterated DPC. Proper amounts of DPC have been weighted to prepare stock water solutions. After surfactant solubilization in D_2O, the stock

* Corresponding author.
E-mail address: lgaliull@kpfu.ru (L.F. Galiullina).

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